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Testicular Dysfunction in Hodgkin's Disease Before and After Treatment

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Over a 7-year period, semen analysis was performed in 92 male patients with Hodgkin's disease prior to therapy. In 67% of patients semen revealed a decreased chance for fertility (i.e. oligozoospermia, asthenozoospermia and/or teratozoospermia). The mean basal levels of follicle-stimulating hormone (FSH), luteinising hormone, testosterone and prolactin were in the normal range. In 77 patients in complete remission after alternating MOPP/ABVD (mechlorethamine, vincristine, procarbazine, prednisone; doxorubicin, bleomycin, vinblastine, dacarbazine), testicular function was assessed. 87% of patients were azoospermic, 9% had semen abnormalities and only 4% were normospermic. Recovery of spermatogenesis was documented in only 17 of 42 (40%) reassessed patients after a median time of 27 months and was generally not affected by pretreatment sperm quality. After chemotherapy, the mean value of FSH [20.45 (S.E. 1.7) mUI/ml] was significantly superior compared with that of the mean pretreatment values. No difference was documented in the mean testosterone and prolactin values tested before and after treatment. Our findings indicate that, of patients with Hodgkin's disease, about half are affected by hypogonadism before starting chemotherapy. By utilising alternating MOPP/ABVD, persistent testicular dysfunction was documented in half of the patients.
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INTRODUCTION

DURING THE past years, many efforts have been made to identify treatments devoid of organ damage such as gonadal failure, which may affect considerably the quality of life in young patients with Hodgkin's disease. Several reports [1–6] have indicated that MOPP (mechlorethamine, vincristine, procarbazine and prednisone) or MOPP-like combinations, i.e. those including a classical alkylating agent and/or procarbazine, induce testicular damage in about 90% of patients. In fact, mechlorethamine and procarbazine have long been considered the responsible agents for germ cell toxicity. A comparative analysis of MOPP and ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) showed permanent gonadal dysfunction only in patients treated with MOPP [7]. The damage of gonadal function induced by cytotoxic drugs is not the only cause of the sexual abnormalities in Hodgkin's disease. Chapman *et al.* [8] reported that gonadal abnormalities may exist in men with Hodgkin's disease before therapy. Furthermore, it has been suggested [9] that hypogonadism in untreated patients with Hodgkin's disease is not simply due to primary testicular failure, but is probably dependent upon a complex abnormality also involving the hypothalamic–pituitary axis, as suggested by the evidence of increased basal levels of prolactin. These abnormalities may be due to an altered dopaminergic tone at hypothalamic sites [8, 9].

The present study was carried out to assess testicular dysfunction in patients with Hodgkin's disease before and after treatment with alternating MOPP/ABVD.

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Table 1. Semen analysis in 92 untreated patients

	Cases	Normospermia	Dyspermia
Total	92	30 (33)	62 (67)
Stage			
I + II	57	19 (33)	38 (67)
III + IV	35	11 (31)	24 (69)
Symptoms			
A	52	21 (40)	31 (60)
B	40	9 (22.5)	31 (77.5)
Fever			
Yes	33	7 (21)	26 (79)
No	59	23 (39)	36 (61)

No. (%).

PATIENTS AND METHODS

Patient population

From June 1982 to December 1990 testicular function was assessed before the start of the chemotherapy program by semen analysis and hormonal evaluation in a total of 92 male patients with biopsy-proven diagnosis of Hodgkin's disease and in whom sperm volume and count, basal forward motility and morphology were available. The main characteristics of the patients are listed in Table 1. All patients were under 45 years of age (median 28, range 18–43 years). According to the Ann Arbor classification, 57 patients were classified as stage I or II, and 35 as stage III or IV. Systemic B symptoms were present in 40 patients, and fever above 38°C was reported in 33 cases. All subjects had normal testicular volume, i.e. larger than 18 ml measured by the Prader orchidometer. No varicocele, cryptorchidism or inflammation of the seminal tract was present. No patient had a previous history of infertility. Additionally, testicular function was evaluated in 77 patients in complete remission after alternating chemotherapy with MOPP/ABVD for a median of 7 cycles (range 6–9). Patients had to give consent for repeat analysis. The median age was 28 years (range 16–48); 37 cases had been classified as stage I or II and 40 cases as stage III or IV. Systemic B symptoms were present in 45 patients and fever in 36. No patient had received irradiation to the paraaortic and/or pelvic nodes. The median time from completion of treatment to gonadal analysis was 5 months (range 1–58). A total of 42 patients accepted to repeat the sperm count at least once.

Semen analysis

Fresh semen was collected by masturbation after a 2–5 day period of abstinence. The following parameters were evaluated: sperm volume and count, basal forward motility and morphology. Following the WHO criteria [10], we classified azoospermia as the absence of spermatozoa in the ejaculate, oligozoospermia as the reduction in sperm count below 20×10^6/ml, asthenozoospermia as the reduction of cells with normal forward motility below 40%, and teratozoospermia as the reduction of cells with normal morphology below 50%. All these seminal abnormalities but azoospermia were categorised as dyspermia.

Hormones

Follicle-stimulating hormone (FSH), luteinising hormone (LH), prolactin and testosterone plasma levels were measured by specific double-antibody RIA methods, using commercial kits (Biodata, Italy) [11–13]. Normal laboratory ranges (95% confidence limits) were as follows: FSH 5–15 mIU/ml, LH 5–15 mIU/ml, prolactin 5–20 ng/ml and testosterone 3–9 ng/ml.

Table 2. Basal hormone levels by disease extent and systemic symptoms, patients vs. control subjects

	FSH* (n = 76)	LH* (n = 76)	Testosterone† (n = 60)	Prolactin† (n = 72)
Total	6.60 (0.48)	7.52 (0.43)	4.21 (0.21)	9.82 (0.73)
Stage				
I + II	6.17 (0.58)	6.96 (0.56)	3.89 (0.23)	9.69 (1.00)
III + IV	7.29 (0.82)	8.43 (0.66)	4.69 (0.40)	10.03 (1.02)
Symptoms				
A	6.48 (0.64)	7.51 (0.60)	4.30 (0.29)	8.63 (0.62)
B	6.78 (0.71)	7.55 (0.63)	4.07 (0.31)	11.79 (1.62)
Fever				
Yes	7.02 (0.80)	7.69 (0.70)	3.99 (0.35)	12.17 (1.90)
No	6.38 (0.59)	7.43 (0.55)	4.32 (0.27)	8.71 (0.57)
Controls‡ (n = 15)	6.00 (0.65)	8.40 (0.52)	4.90 (0.26)	8.34 (0.70)

Mean (S. E.)*mIU/ml, †ng/ml. ‡ See [7].
FSH = follicle-stimulating hormone, LH = luteinising hormone.

Statistical analysis

Differences on proportions were assessed by use of the χ^2 test; the paired t test was used to assess differences between pretreatment and post-treatment values.

RESULTS

Pretreatment evaluation

Semen analysis. As shown in Table 1, 67% of patients had an abnormal semen sample before starting treatment: 28 patients showed a single semen abnormality whereas the other 34 patients showed multiple abnormalities. The most frequent abnormalities were the reduction in progressive motility (68%) and in the number of sperm cells with normal morphology (71%). Oligozoospermia was present in 34% of the semen samples. The main clinical features, i.e. age, stage, B symptoms and fever were analysed to assess a possible relationship with the pretreatment dyspermia, but none was found to be significantly correlated with sperm abnormalities. 22% of patients with B symptoms had a normal semen sample, whereas 40% of asymptomatic patients were normospermic ($P = 0.07$). By analysing the single symptoms, 26 of 33 (79%) patients presenting with fever had abnormal semen samples vs. 36 of 59 (61%) without pyrexia.

Before the diagnosis of Hodgkin's disease, 23 patients had fathered children.

Hormonal evaluation. Table 2 shows the basal levels of FSH, LH, testosterone and prolactin of the patients with Hodgkin's disease. The mean basal hormone levels were not different from those observed in 15 healthy men [7]. Basal hormone levels were not affected by the main patient characteristics, such as stage, systemic symptoms and fever. Of note, there was also no difference in the mean basal hormone levels whether or not patients presented abnormal semen sample.

Post-treatment evaluation

Semen analysis. A total of 77 patients were examined after a median time of 5 months (range 1–58) from the completion of therapy. Semen analysis revealed that 67 (87%) were azoo-

Table 3. Semen analysis in 77 patients after MOPP/ABVD

	Cases	Azoospermia	Dyspermia	Normospermia	Recovered/reassessed
Total	77	67 (87)	7 (9)	3 (4)	17*/42
No. cycles					
≤ 6	36	29 (81)	5 (14)	2 (5)	11/19
> 6	41	38 (93)	2 (5)	1 (2)	6/23
Age (yr)					
≤ 30	44	40 (91)	3 (7)	1 (2)	9/23
> 30	33	27 (82)	4 (12)	2 (6)	8/19

No. (%).
*Dyspermia 12, normospermia 5.

spermic, 7 were dyspermic and that the remaining 3 patients showed a normal sperm count, respectively (Table 3). 63 patients were evaluated during the first 12 months from the end of therapy. Of the remaining 14 patients, 11 were evaluated between 13 and 31 months from the treatment completion and 3 at 45, 51 and 58 months. The number of treatment cycles delivered (6 vs. >6), and age, i.e. ≤30 vs. over 30 years, at the time of starting treatment had no apparent influence on frequency and type of gonadal damage. Recovery of spermatogenesis occurred within a median of 27 months (range 23–60) from the end of therapy in 17 of 42 patients in whom the sperm count was reassessed at least once. Only in 1 case was recovery documented after more than 5 years. In 5 cases a full recovery was observed, whereas 12 patients showed only a partial recovery, i.e. oligo-asthenozoospermia (range 2.2–4.6×10^6/ml). 55 of 77 patients were evaluated before and after treatment. As reported in Table 4, presence or absence of initial sperm abnormalities failed to influence either the frequency of azoospermia (86% vs. 85%) or its recovery (6 of 12 and 6 of 17).

Hormonal evaluation. After completion of chemotherapy, FSH, LH, testosterone and prolactin plasma levels were determined in 44 patients. The mean FSH and LH levels were significantly higher ($P<0.001$ and $P<0.01$, respectively) than the mean values in the control group of healthy males, while prolactin and testosterone mean levels did not show a significant comparative difference. In 31 patients hormonal evaluation was performed before and after chemotherapy. The mean FSH levels [20.45 (S.E. 1.70) vs. 6.21 (0.52); $P<0.0001$] as well as the mean LH levels [11.97 (1.00) vs. 7.54 (0.61); $P<0.0001$] were significantly higher after chemotherapy compared to pretreatment values. By contrast, the mean levels of testosterone and prolactin were not significantly influenced by treatment. Among patients who had a recovery of spermatogenesis, FSH levels returned to the normal range in 2 of 10 cases, while in the other cases FSH remained high despite recovery of testicular function.

Table 4. Frequency of testicular failure after MOPP/ABVD in 55 patients by fertility status before treatment

	Fertility status before treatment	
	Normospermia (n = 21)	Dyspermia (n = 34)
Azoospermia (%)	86	85
Dyspermia (%)	14	9
Normospermia (%)	0	6
Months* (range)	6 (3–29)	5 (1–28)
Recovered/reassessed	6/12†	6/17‡
Months* (range)	29.5 (24–60)	25 (23–43)

*Median time from end of therapy.
†Normospermia 3, dyspermia 3.
‡Normospermia 1, dyspermia 5.

DISCUSSION

According to the results previously reported by other authors [9] as well as by ourselves [14], this study confirms that men with Hodgkin's disease can often show gonadal dysfunction even before the start of chemotherapy. These findings may suggest that Hodgkin's disease *per se* can cause sterility. The mechanisms by which Hodgkin's disease may induce gonadal failure remain to be further clarified. However, the evidence of normal mean FSH levels, as reported in this and other studies [9], would exclude primary gonadal damage and suggest that the hypothalamic–pituitary disorder may be responsible for sterility in untreated patients. Additionally, an enhanced prolactin secretion itself may affect spermatogenesis [9, 15]. However, in this study we were unable to confirm an increased basal prolactin production in Hodgkin's disease.

After MOPP or MOPP-like combination chemotherapy, testicular dysfunction was documented in almost all patients (>95%) and recovery of spermatogenesis occurred in about 20% of cases [1–7]. The degree of testicular damage was clearly related to the total amount of drugs administered and three courses of MOPP could represent a limiting gonadal exposure for the recovery of spermatogenesis [16]. The frequency of azoospermia was significantly lower when combinations did not include alkylating agents and/or procarbazine [7, 17–19]. With ABVD, azoospermia was documented in 36% of cases and recovery of spermatogenesis in 13 of 13 (100%) patients [20]. These data are in agreement with those reported by the Stanford group with VBM (vinblastine, bleomycin and methotrexate) [21]. Additionally, Meistrich *et al.* [22] reported that in 78% of patients with osteosarcoma treated with doxorubicin, dacarbazine and cisplatin with or without other drugs, sperm counts returned to normal values and full recovery was not influenced by the doses of either doxorubicin or dacarbazine. Our findings indicate that, by utilising alternating MOPP and ABVD, testicular dysfunction occurs in 87% of patients and recovery of spermatogenesis is possible in only 40% of cases. These results are intermediate between those achieved with MOPP or ABVD alone, respectively, and suggest a decrease in testicular damage by reducing the total number of MOPP courses administered. Nevertheless, gonadal toxicity induced by alternating MOPP and ABVD was definitely higher than that achieved after ABVD alone. Chemotherapy-induced sterility is due to a primary testicular damage as shown by the increased levels of FSH. However, recovery of spermatogenesis may occur even in the presence of persistently elevated FSH values. Therefore, the determination of FSH levels alone is not enough to document the possible recovery. Present study also suggests that there were no clinical parameters which could be predictive of chemotherapy-induced sterility. In the same way, as previously reported by Redman *et al.* [23], semen characteristics before the onset of therapy do not seem to be predictive for the recovery of testicular function.

Table 5. Hormone levels related to fertility status after MOPP/ABVD

Fertility status	Cases	FSH (mIU/ml)	LH (mIU/ml)	Testosterone (ng/ml)	Prolactin (ng/ml)
Total	46	23.81 (1.80)	12.92 (1.09)	5.24 (0.34)	11.24 (0.97)
Azoospermia	39	24.78 (1.99)	13.09 (1.19)	5.33 (0.40)	11.14 (1.02)
Dyspermia	6	19.33 (4.41)	11.00 (3.23)	4.42 (0.40)	11.25 (3.61)
Normospermia	1	12.9	16.1	7.3	15

*Mean (S.E.).

In conclusion, this case series substantiates the finding that young men with Hodgkin's disease have an underlying gonadal dysfunction independent of the effect of chemotherapy. Since the majority of patients have subfertile sperm concentration after treatment, artificial insemination becomes an important option. However, the deficient quality of the cryopreserved semen may represent a barrier to successful artificial inseminations. Furthermore only 20–30% of patients with Hodgkin's disease meet the criteria for cryopreservation, compared with 60% of male controls [23, 24]. Consequently, semen cryopreservation and artificial insemination offer a solution only to a very limited fraction of patients who become azoospermic after treatment. A hopeful alternative would be to design newer chemotherapy regimens associated with minimal gonadal toxicity but with a therapeutic activity similar to the optimal conventional regimens. However, the use of gonadotropin-releasing hormone analogues or testosterone failed to show any decrease in testicular damage induced by chemotherapy perhaps for the long time required for effective suppression of spermatogenesis before starting of chemotherapy [25–27]. Therefore, the most suitable alternative to reduce therapy-related sterility remains either the administration of a few cycles of MOPP or MOPP-like combinations as in the alternating MOPP/ABVD regimen or the choice of ABVD or VBM alone for patients with early stage Hodgkin's disease.

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